

Chromosomal Abnormalities Are Major Prognostic Factors in Elderly Patients With Multiple Myeloma: The Intergroupe Francophone du Myélome Experience

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ABSTRACT

Purpose

Chromosomal abnormalities, especially t(4;14) and del(17p), are major prognostic factors in patients with multiple myeloma (MM). However, this has been especially demonstrated in patients age < 66 years treated with intensive approaches. The goal of this study was to address this issue in elderly patients treated with conventional-dose chemotherapy.

Patients and Methods

To answer this important question, we retrospectively analyzed a series of 1,890 patients (median age, 72 years; range, 66 to 94 years), including 1,095 with updated data on treatment modalities and survival.

Results

This large study first showed that the incidence of t(4;14) was not uniform over age, with a marked decrease in the oldest patients. Second, it showed that both t(4;14) and del(17p) retained their prognostic value in elderly patients treated with melphalan and prednisone-based chemotherapy.

Conclusion

t(4;14) and del(17p) are major prognostic factors in elderly patients with MM, both for progression-free and overall survival, indicating that these two abnormalities should be investigated at diagnosis of MM, regardless of age.

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INTRODUCTION

Despite tremendous improvements in the outcome of patients with multiple myeloma (MM) during the last decade, most encounter relapse. However, large heterogeneity is observed; some patients present with highly refractory disease, whereas others may enjoy up to 15 years disease free. This heterogeneity can be predicted, at least in part, thanks to prognostic factors. Among them, the most powerful is cytogenetics. MM is characterized by many chromosomal abnormalities, present in up to 95% of patients (based on recent SNParray reports).¹ Several recurrent chromosomal changes have been described, the most frequent being hyperdiploidy (50% to 60% of patients), monosomy 13 or del(13) (45%), 1q gains (30% to 35%), t(11;14) (20%), and t(4;14) (15%).²⁻⁵ Some of these abnormalities have been shown to dictate patient outcome.⁶⁻⁹ This is especially true for t(4;14) and del(17p). However, most of these data (both for incidence and prognos-

tic value) have been obtained in the youngest patients (usually age < 65 years), treated with high-dose melphalan. Whether these data are relevant in elderly patients is not known. For instance, in acute lymphoblastic leukemia, Philadelphia chromosome incidence is much higher in older patients. To address this issue, we searched the Intergroupe Francophone du Myélome (IFM) database for patients age > 65 years analyzed for the most common chromosomal rearrangements and with available clinical data regarding treatment modalities and outcome.

PATIENTS AND METHODS

The IFM cytogenetic network centralizes patient samples in a unique laboratory for chromosomal analyses. All the patients signed an informed consent form allowing biologic studies. Bone marrow samples were shipped overnight. On receipt, bone marrow mononuclear cells were separated.

Then, plasma cells were sorted using anti-CD138 immunomagnetic systems (MiltenyiBiotec, Paris, France, or StemCell Technologies, Vancouver, British Columbia, Canada) according to manufacturer instructions. After sorting, plasma-cell purity was checked morphologically. After fixation in Carnoy's fixative, sorted plasma cells were analyzed by fluorescence in situ hybridization (FISH), as previously described.⁹ Specific probes for chromosome 13 (q14 band) and chromosome 17 (p13 band) and for detection of t(4;14) translocation were purchased from Abbott Molecular (Des Plaines, IL). As previously described, FISH results were considered abnormal if deletion was observed in > 30% of plasma cells for chromosome 13, in > 60% of plasma cells for chromosome 17, and, if translocation was observed, in > 30% of plasma cells for t(4;14).⁹

Patients were treated with different schemas: 434 patients were treated with a combination of melphalan, prednisone, and thalidomide (MPT); 246 patients received MP, mostly within the IFM 99-06 trial (arm A)¹⁰; and 168 patients were treated with high-dose melphalan (200 mg/m²; of note, this group of patients was significantly younger than the rest of the cohort [median age, 66 years]; 118 patients received lenalidomide plus dexamethasone; 84 patients received a combination of MP and bortezomib (MPV)¹¹; and finally, 45 patients received intermediate-dose melphalan (100 mg/m²) within the IFM 99-06 trial (arm C).¹⁰

The primary end point was the correlation with survival from time of diagnosis. Kaplan-Meier curves for progression-free survival (PFS; defined by time between diagnosis and occurrence of progression, relapse, or death) and overall survival (OS) were plotted and compared using the log-rank test. Prognostic factors for PFS and OS were determined using the Cox proportional hazard model for covariate analysis. Statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

We found 1,890 patients age > 65 years with newly diagnosed symptomatic MM and FISH data after searching the IFM database; median age was 72 years (range, 66 to 94 years). Patients were classified in two groups: those age 66 to 75 years (*n* = 1,239), and those age > 75 years (*n* = 651). Incidences of the three chromosomal aberrations are summarized in Appendix Table A1 (online only). In the two groups, we observed statistically significant differences for incidence of del(13) and t(4;14), with lower incidence in older patients. Similarly, when compared with a group of 2,347 patients age < 66 years, this lower frequency was confirmed, with incidences decreasing with age (Appendix Table A1, online only). In contrast, incidence of del(17p) was remarkably stable within the three groups.

For prognostic analyses, we searched the IFM database for patients with data on treatment modalities and outcome. We found a total of 1,095 patients corresponding to these criteria. When compared with the 795 patients without follow-up data, these 1,095 patients were not significantly different with regard to age, sex, or incidence of del(13), t(4;14), or del(17p). Before analyzing the prognostic values of chromosomal abnormalities, we first analyzed PFS and OS according to protocol strategies. On the basis of not significantly different outcomes, patients were grouped within three categories: those treated with MPT, those treated within the IFM 99-06 trial (arms A and C), and others. Then, statistical analyses of the impact of

Table 1. Prognostic Value of Chromosomal Abnormalities for PFS*

Abnormality	HR	95% CI	<i>P</i>
del(13)	1.31	1.04 to 1.64	.02
t(4;14)	2.03	1.49 to 2.76	< .001
del(17p)	1.96	1.39 to 2.75	< .001

Abbreviations: HR, hazard ratio; PFS, progression-free survival.

*Multivariate analyses, stratified according to treatment.

chromosomal abnormalities on outcome were stratified according to treatment. In univariate analyses, all three abnormalities displayed a significant *P* value for both PFS and OS, even though the impact of del(13) on OS was marginally significant (Appendix Tables A2 and A3, online only). The prognostic value of t(4;14) and del(17p) was retained in patients treated with novel therapies, such as MPV or lenalidomide plus dexamethasone. Similar results were found in elderly and very elderly subgroups (with 75-year age cutoff). In multivariate analyses, t(4;14) and del(17p) were independent predictors of short PFS and OS duration, whereas del(13) was only marginally significant for PFS prediction but not for OS (Tables 1 and 2; Figs 1 to 4).

DISCUSSION

During the past decade, the outcome of patients with MM has been dramatically improved, essentially because of the availability of novel drugs such as thalidomide, bortezomib, and lenalidomide. On the basis of recent data (personal IFM data), we can estimate that half of the patients age < 65 years will live > 10 years after diagnosis. For older patients, the estimate is 5 to 6 years. However, these numbers are medians and do not reflect the huge heterogeneity observed in MM outcome. Thus, the availability of reliable prognostic factors is important to predict survival and to try to adapt patient/family information—and, it is hoped, treatment modalities—to this expected survival. As is usual in hematologic malignancies, the most powerful prognostic factors are chromosomal changes observed in the tumor clone. In MM, the most important prognostic changes are t(4;14) and del(17p). Although bortezomib may improve the outcome of patients presenting with t(4;14) translocation,^{11,12} these patients still experience shorter outcome than those with standard-risk cytogenetics.¹³ The situation is even more dramatic for patients with del(17p), for whom no improvement has been achieved in the past years.

However, a large majority (if not all) of the data addressing the issue of prognostic impact of chromosomal abnormalities in MM have been obtained in young patients treated with high-dose chemotherapy. Whether these data are also valid in the elderly population is

Table 2. Prognostic Value of Chromosomal Abnormalities for OS*

Abnormality	HR	95% CI	<i>P</i>
del(13)	1.12	0.83 to 1.53	.45
t(4;14)	1.89	1.28 to 2.80	< .001
del(17p)	2.14	1.39 to 3.28	< .001

Abbreviations: HR, hazard ratio; OS, overall survival.

*Multivariate analyses, stratified according to treatment.

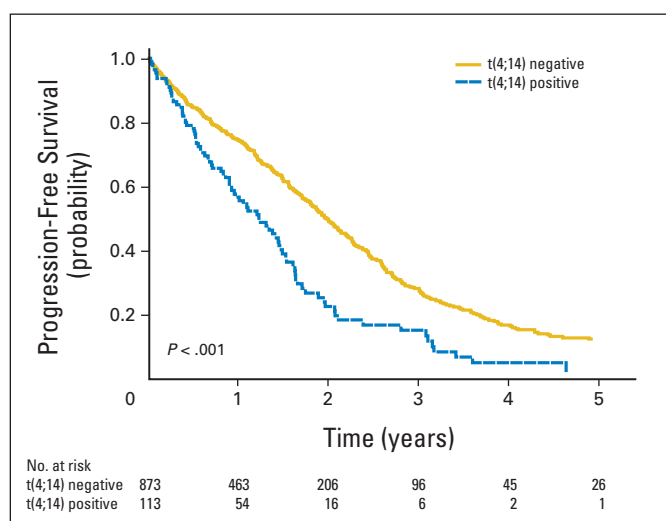


Fig 1. Progression-free survival curves according to presence of t(4;14).

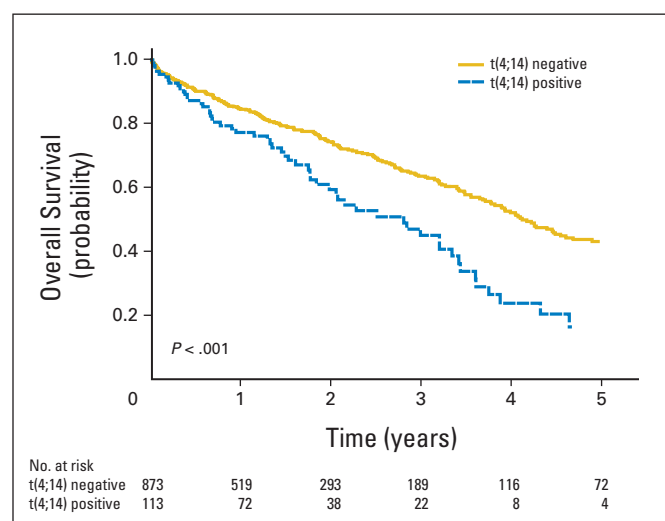


Fig 3. Overall survival curves according to presence of t(4;14).

an open question. To answer this question, we analyzed a large cohort of patients with a median age of 72 years (range, 66 to 94 years). We first looked at the incidence of major chromosomal changes. Surprisingly, we found striking differences when compared with younger patients (Appendix Table A1, online only). Although the incidence of del(17p) was remarkably stable in all age groups, we observed a lower incidence of del(13) and t(4;14) in the oldest patients. It is quite difficult to speculate on the reasons for these differences. Would oncogenesis of MM be different in the elderly population? One hypothesis could be that MM in the elderly is diagnosed after a longer phase of monoclonal gammopathy of undetermined significance (MGUS), which is more frequent in elderly patients. Even if conflicting data are reported regarding the incidence of t(4;14) in MGUS, we can speculate that those patients will evolve more rapidly to MM, and thus, t(4;14) may be more frequent in younger patients.

Because this cohort was not enrolled onto a single clinical trial, treatment modalities were quite heterogeneous. The largest cohort was treated with MPT, according to or within the IFM 99-06 trial (18

months of treatment). We confirm that even outside of a clinical trial, this combination provides a better outcome than the standard MP combination. The best results were obtained with high-dose melphalan (200 mg/m²), but this population was highly selected, with a median age of 66 years. According to these results, we performed a statistical analysis stratified on treatment modalities. Whatever the treatment was, both t(4;14) and del(17p) were associated with shorter PFS and OS. The median PFS for patients with t(4;14) and del(17p) was 14 ($P < .001$) and 11 months ($P < .001$), respectively, as compared with 24 months for patients lacking both abnormalities; similarly, the median OS was 32 ($P < .001$) and 19 months ($P < .001$), respectively, as compared with 50 months. Thus, these two specific chromosomal changes retained the same prognostic value as for younger patients.

These findings may have therapeutic implications. Even though t(4;14) and del(17p) share poor prognosis value, several reports support that bortezomib might be the drug of choice for patients with t(4;14). Of course, it does not totally overcome the prognostic value of

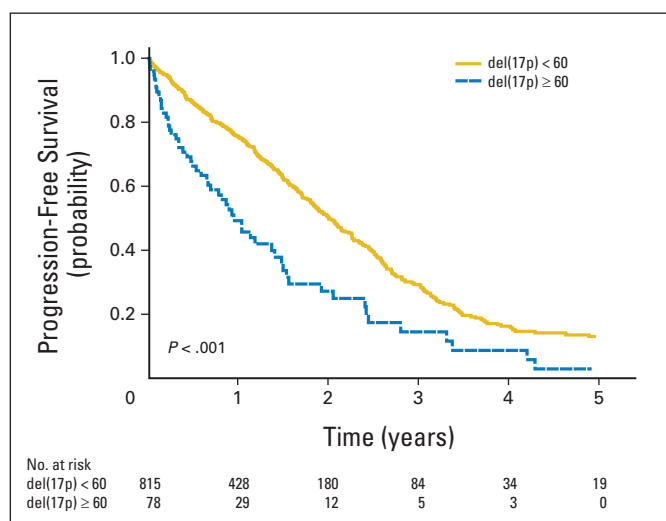


Fig 2. Progression-free survival curves according to presence of del(17p).

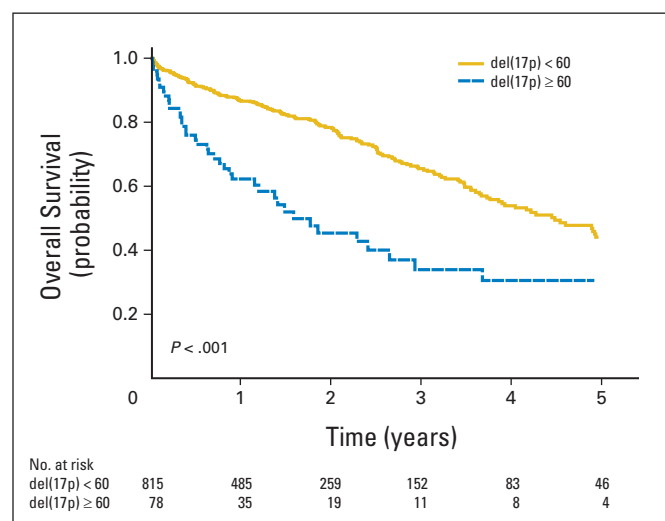


Fig 4. Overall survival curves according to presence of del(17p).

translocation, but it seems to improve the outcome of patients. Because of the small number of t(4;14)-positive patients treated with the MPV combination in our series, it was not possible to compare their outcome with that of patients treated with MPT. Otherwise, on the basis of previously published reports, the MPV combination could be the first choice for those patients with t(4;14). In contrast, no treatment has been shown to improve the outcome of patients with del(17p). For instance, the median OS for these patients was only 19 months in this series. In conclusion, even if we found a lower incidence of t(4;14) in the oldest patients, both t(4;14) and del(17p) were associated with poor outcome in this cohort of elderly patients with MM, strengthening the importance of analysis at diagnosis, even in the oldest population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix**Table A1.** Incidence of Chromosomal Abnormalities According to Age Group

Abnormality	Age Group (years)			<i>P</i>
	< 66 (%)	66 to 75 (%)	> 75 (%)	
del(13)	45	43.6	37	.004
t(4;14)	14.3	10.9	8.3	< .001
del(17p)	6	5.9	6.1	NS

Abbreviation: NS, not significant.

Table A2. Prognostic Value of Each Chromosomal Abnormality for PFS*

Abnormality	HR	95% CI	<i>P</i>
del(13)	1.41	1.19 to 1.68	< .001
t(4;14)	1.88	1.49 to 2.37	< .001
del(17p)	2.03	1.53 to 2.69	< .001

Abbreviations: HR, hazard ratio; PFS, progression-free survival.

*Univariate analyses, stratified according to treatment.

Table A3. Prognostic Value of Each Chromosomal Abnormality for OS*

Abnormality	HR	95% CI	<i>P</i>
del(13)	1.24	1.01 to 1.53	.045
t(4;14)	1.85	1.39 to 2.46	< .001
del(17p)	2.38	1.69 to 3.34	< .001

Abbreviations: HR, hazard ratio; OS, overall survival.

*Univariate analyses, stratified according to treatment.